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A New and More Practical Approach to the Synthesis of the Precursor of SC-84536, A Selective Inducible Nitric Oxide Synthase Inhibitor

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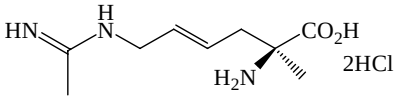
SC-84536, a selective inhibitor of inducible nitric oxide synthase (INOS), is targeted for the treatment of osteoarthritis, neuropathic pain and asthma. This report describes our effort toward developing an alternative synthetic route for preparation of SC-84536. In the process, we also developed a new and simple method for the preparation of phthalimide 6, a potentially useful synthon.

Keywords: Synthesis, SC-84536, Inducible nitric oxide synthase, Inhibitor, Phthalimide

INTRODUCTION

SC-84536, was targeted as a selective inhibitor of inducible nitric oxide synthase (INOS) which may be useful in the treatment of osteoarthritis, neuropathic pain and asthma [1]. An early method [2] for the preparation of SC-84536 was deemed impractical and thus an alternative approach was sought.



SC-84536

Some of the problems associated with the original synthesis included: 1) The alkylation reaction to produce **1** was messy and proceeded in only 30% yield. 2) The 3-methyl-4*H*-[1,2,4]-oxadiazol-5-one in **1** is unstable, expensive and posed a safety risk for scaling this chemistry. 3) The allyl bromide **1** during the alkylation reaction with Schiff base **3** (Scheme 1) was very prone to elimination to give **2** and thus preparation of the carbon skeleton **4** proved not to be consistently reproducible and thus could not be scaled up to prepare large quantities of material. Because of these issues, our objective was to devise an alternative approach for building the carbon framework that would have a better chance of being scaled.

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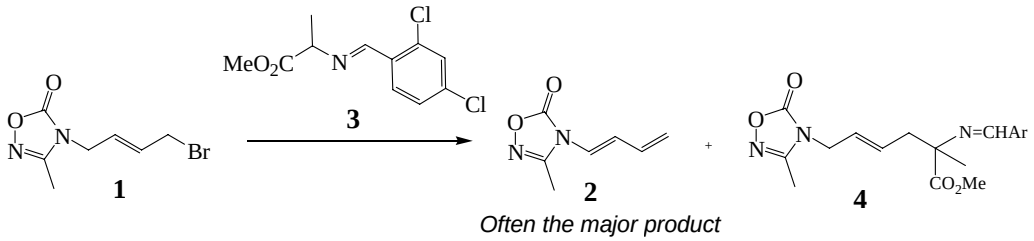
EXPERIMENTAL

2-(2-Hydroxy-but-3-enyl)-isoindole-1,3-dione 6. Phethalimide (29.4 g), the cyclic carbonate **5** (25 ml) and K_2CO_3 (1 g) were mixed together in 100 ml of dimethylsulfoxide (DMSO) and was slowly heated to 105 °C. At 102 °C slow evolution of CO_2 was observed. The mixture was heated for 6 h and then cooled to room temperature and acidified with 10% HCl. To the resulting mixture, H_2O (160 ml) was slowly added upon which, after seeding, crystallization of the desired product **6** occurred. The mixture was cooled in an ice bath and then filtered and dried to afford 28.2 g (65% yield) of the phthalimide. ^{1}H NMR ($CDCl_3$) δ 7.88 (Ar, m, 2H), 7.75 (Ar, m, 2H), 5.92 (=CH, m, 1H), 5.39



Scheme 1

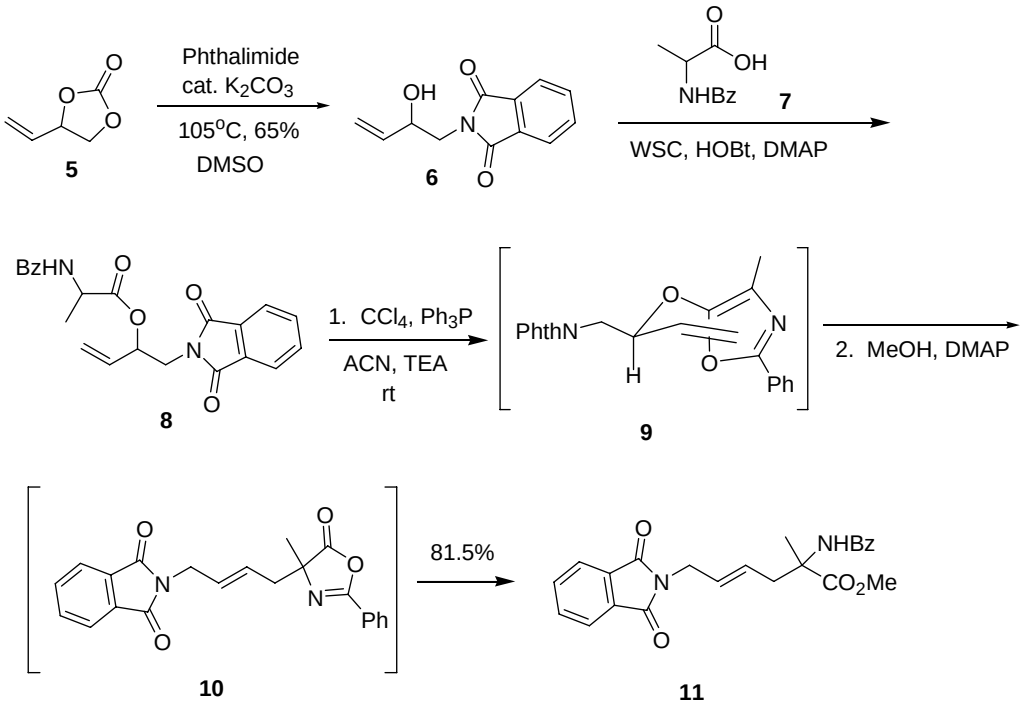
(=CH_2, d, *J* = 17.2, 1H), 5.21 (=CH_2, d, *J* = 8.5, 1H), 4.49 (HC-O-, m, 1H), 3.86 (-CH_2N, m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ (ppm) 168.8, 137.2, 134.1, 131.9, 123.4, 116.8, 71.2, 43.8 ppm.

2-Benzoylamino-propionic acid 1-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-allyl ester 8. A mixture of the imide **6** (10.0 g), the acid **7** (11.1 g), DMAP (1.23 g) and 1.3 g of hydroxybenzotriazole (HOBt), in 100 ml of THF was treated with 27 g of water soluble carbodiimide at <29 °C. The reaction mixture becomes thick after 20 min. The mixture was heated to 45 °C overnight. Ethyl acetate (EtOAc) and aqueous $NaHCO_3$ were added and the product extracted. The reaction failed to go to completion. The product was purified by chromatography on silica gel with 40% EtOAc/hexanes to give 10.2 g of the desired ester **8**. The NMR spectrum was quite messy because of the formation of 2 diastereoisomers. The diastereoisomeric mixture was used without further attempts for the separation of diastereomers at next step of synthesis.

2-Benzoylamino-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-methyl-hex-4-enoic acid methyl ester 11. The ester **8** (1.0 g, 2.55 mmol), in 10 ml of CH_3CN was treated with 0.5 ml (5.2 mmol) of CCl_4, 0.83 ml (6.0 mmol) of triethylamine and 1.34 g (5.1 mmol) of Ph_3P at room temperature. When TLC shows the disappearance of the starting material, MeOH, 1 ml of triethylamine and cat. 4-dimethylaminopyridine (DMAP, 50 mg) were added to the reaction mixture and was heated to 50 °C for 3 h. The crude mixture was poured into 5% aqueous solution of HCl and the product was extracted with EtOAc. Chromatography on silica gel with 40% EtOAc/hexanes gives 880 mg (81.5%) of the desired ester **11**. ^{1}H NMR ($CDCl_3$) δ 7.69 (Ar, m, 6 H), 7.37 (Ar, t, *J* = 7.2 Hz, 1H), 7.28 (Ar, t, 2H, *J* = 7.7 Hz) 5.58 (CH=CH, m, 2H), 4.13 (CH_2, d, *J* = 6.7 Hz, 2H), 3.67 (MeO, s, 3H), 2.90 (CH, dd, *J* = 6.9, 13.7 Hz, 1H), 2.68 (CH, dd, *J* = 6.9, 13.7 Hz, 1H), 1.62 (CH_3, s, 3H) ppm. ^{13}C NMR ($CDCl_3$) δ 174.3, 167.7, 166.5, 134.4, 133.9, 131.9, 131.4, 128.9, 128.6, 128.4, 126.8, 123.2, 60.0, 52.7, 39.3, 38.6, 22.8 ppm.

RESULTS AND DISCUSSION

Our general plan was to take advantage of the fact that chirality is readily transferred in a Claisen rearrangement. Thus, the plan was to prepare a precursor such as **8** which would transfer chirality to the new quaternary center. In the event, a new and more efficient route was developed to the known alcohol **6** (Scheme 2). Here the readily available carbonate **5** [3] was treated with phthalimide in DMSO with a catalytic amount of K_2CO_3 and heated to 105 °C at which point the reaction starts to release CO_2. When CO_2 evolution is complete the mixture is cooled and water is slowly added to crystallize out the imide **6**. Note that this result is in contrast to Trost's palladium catalyzed reaction with butadiene epoxide which places the phthalimide at the 2-postion [4]. Esterification of **6** with the acid **7**, prepared from alanine, gives the desired ester **8** as a mixture of isomers. Since the alanine chiral center was to be destroyed *via* enolization this was of no consequence. Attempts to form the zinc enolate and induce rearrangement according to the literature [5] failed; perhaps due to the reactivity of the imide in the presence of the nucleophilic enolate. An alternative approach was to prepare an oxazole under mildly basic conditions and effect rearrangement according to the method of Steglich [6]. The oxazole **9** was prepared *in situ* using CCl_4, Ph_3P, triethylamine (TEA) and CH_3CN which resulted in spontaneous rearrangement to give azlactone **10** that was not isolated but



5 **6** **8** **9** **10** **11**

Scheme 2

converted directly to the ester **11** by treatment with MeOH/4-dimethylaminopyridine (DMAP) in 81.5% yield. Azlactone **10** was not isolated because these derivatives may also undergo 3,3-sigmatropic rearrangements [6].

At this point we had a simple approach to the key carbon framework of our INOS inhibitor that resolved the problems with the alkylation of **2**. In the process we also developed a new and simple method for the preparation of phthalimide **6**, a potentially useful synthon.

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